REMARKS

Claims 29-39 and 41-49 presently appear in this case. Claims 44 and 45 have been withdrawn from consideration. No claims have been allowed. The Official Action of October 27, 2010, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a pH-independent extended release dosage form of venlafaxine hydrochloride. The venlafaxine hydrochloride is coated on a nonpareil core over which is coated a controlled release layer, which is a controlled release polymer optionally mixed with a plasticizer. The controlled release layer permits controlled release of the venlafaxine hydrochloride over an approximately 24 hour period. An intermediate isolating layer may also be present. Preferably, the pH-independent extended release dosage form has dissolution characteristics that are equivalent to those of the venlafaxine hydrochloride dosage forms sold under the proprietary name EFFEXOR XR.

The examiner states that claims 44 and 45 have been withdrawn from consideration because they lack unity with the invention originally claimed. The only ground that the examiner gives for this statement is that the originally presented claims

pertain to composition claims only whereas claims 44 and 45 pertain to method claims. The examiner states that it is irrelevant that the present case is subject to unity of invention practice because election by original presentation also applies to unity of invention practice. This restriction requirement is respectfully traversed.

It is significant that the present application is subject to unity of invention practice as the examiner cannot rely upon election by original presentation unless the newly added claims lack unity of invention with the originally claimed invention. Here, the newly added claims do not lack unity of invention with the originally presented claims. The fact that the originally presented claims pertain to composition claims whereas claims 44 and 45 pertain to methods for use of the composition, does not automatically mean that they lack unity of invention. To the contrary, the examiner's attention is invited to 37 CFR §1.499, which states that the examiner can only find lack of unity of invention in a national stage application under the requirements of 37 CFR §1.475. 37 CFR §1.475(b)(2) states:

> [A] national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to

> one of the following combinations of categories:
> ….
>
> (2) A product and process of use of said product…

Accordingly, it is very clear according to the applicable regulations that a product and a process of use share unity of invention. The fact that the composition was elected by original presentation does not change the fact that the method of use of that composition shares unity of invention therewith and cannot be considered to be a separate invention that was not elected. Accordingly, reconsideration and withdrawal of this unity of invention requirement and action on all of the claims now present in the case are respectfully urged.

Claim 47 has been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claim is rejected because it does not identify the structure, material or acts set forth in the specification that would be capable of carrying out the functional properties recited in the claims, such as "equivalent to the dissolution characteristics to EFFEXOR XR." The examiner states that it appears from the specification that these claimed functional properties are achieved from specific

formulations that contain specific ingredients, such as polyvinyl pyrrolidine, ethyl cellulose and dibutyl sebacate. The examiner states that applicant's arguments against Heiligenstein established that a reference having all of the ingredients, such as hydrophilic polymer, hydrophobic polymer and plasticizer, can fail to be bioequivalent to EFEXOR XR. Accordingly, the examiner states that the ingredients which make up the formulation must be clearly and positively specified in order to place one of skill in the art in possession of the claimed composition with the desired properties, as it is precisely these ingredients that determine the desired properties and without which, one would not be able to replicate the invention. This rejection is respectfully traversed.

Claim 47 has now been amended to specify the preferred components of the various layers. Furthermore, the reference to whether the layer is hydrophilic or hydrophobic is no longer relevant in light of specifying the ingredients, so this language has been deleted in favor of a functional description, i.e., "isolating layer" and "controlled release polymer." Thus, this claim now specifies that the active principle is venlafaxine hydrochloride and the pharmaceutical has three layers. A nonpareil inert core is coated with the venlafaxine

hydrochloride, which is optionally connected to a binder in an amount of 0.5 to 10 weight percent. The claim goes on to state that the second layer is an isolating layer, specifying the particular possible components of this layer, which layer comprises 0.5 to 10% based on the total weight of the dosage form. The claim further specifies that the outer layer is a controlled release layer comprising a controlled release polymer mixed with a plasticizer and specifying the possible components for the controlled release polymer, the controlled release polymer comprising 2-15 weight percent and the plasticizer being present in 0.1 to 2 weight percent. The claim then specifies that the parameters are selected so as to control release of the venlafaxine hydrochloride so as to obtain the desired pH- and rpm-independent *in vitro* dissolution specifications.

The examiner has conceded on pages 4 and 5 of the Office action that it appears from the specification that the claimed functional properties are achieved from specific formulations that contain specific ingredients and that it is precisely these ingredients that determine the desired properties and without which one would not replicate the invention. As the specific ingredients from the specification are now claimed, the claims as presently amended are fully

supported by the application as filed. Accordingly, the written description is sufficient to support the claim as presently amended. Reconsideration and withdrawal of this rejection are respectfully urged.

Claim 47 has been rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The examiner states that one skilled in the art would not know the metes and bounds of "the dissolution profile of EFFEXOR XR." The examiner suggests limiting the claim to the actual dissolution profile rather than the EFFEXOR XR trade name.

In accordance with the examiner's suggestion, claim 47 has now been amended to substitute the dissolution profile from the table in the specification and to avoid use of the EFFEXOR XR trade name. Accordingly, it is believed that this rejection has been obviated. Reconsideration and withdrawal thereof is respectfully urged.

Claims 29-43 have been rejected under 35 USC 103(a) as being unpatentable over Heiligenstein. The examiner states that the recitations "pH-independent" and "extended release" have not been given patentable weight because the recitations occur in

the preamble. The examiner states that applicant's claims are broad in reciting the genus of "hydrophilic polymer" and "hydrophobic polymer" and "binder," whereas Heiligenstein teaches using species that are in these genera. The examiner states that the HPMCAS used by Heiligenstein is a "hydrophobic polymer." This rejection is respectfully traversed.

The claims have now been amended to add a "wherein" clause at the end specifying that the layers cause the venlafaxine hydrochloride to be released "in a pH-independent manner over an approximately 24 hour period after oral administration." Thus, this important distinction over Heiligenstein is now in the claim and not merely in the preamble.

Furthermore, the claims have been amended in order to specify the preferred components of the isolating layer as well as the controlled release polymer layer. The examiner has clearly taken the position at the first two lines of page 5 of the Office action that it is precisely these ingredients that determines the desired properties and without which, one could not replicate the invention. Thus, the present claims clearly define over Heiligenstein and would not be obvious therefrom, either alone or in combination with any other art of record.

Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 29-43, and 46-48 have been rejected under 35 USC 103(a) as being unpatentable over Oshlack in view of Sherman and Palomo Coll, as evidenced by an FDA Guidance for Industry (2002), hereinafter "FDA." The examiner states that Oshlack teaches an extended release drug composition with all of applicant's claimed layers but not teaching use of venlafaxine hydrochloride as the drug or the use of a separation layer such as polyvinylpyrrolidone. The examiner states that Sherman teaches a composition for extended release of venlafaxine hydrochloride using a film coating of ethyl cellulose to retard dissolution for extended release. The examiner states that Palomo Coll teaches that separation layers made from hydroxypropylmethylcellulose and polyvinylpyrrolidone are well known in the art. The examiner considers that it would have been obvious to incorporate venlafaxine into Oshlack's composition in order to improve the stability of the venlafaxine composition and still have 24 hour extended release of the drug. The examiner considers that it would have been obvious to incorporate a separation layer into Oshlack's composition as polyvinylpyrrolidone and hydroxypropylmethylcellulose are

functional equivalents used as separation layers in drug formulation. The examiner considers that optimization of parameters is a routine practice that would have been obvious in order to achieve, for example, a drug release rate to meet the requirement of the FDA publication for a generic drug to be bioequivalent by dissolution studies to the reference drug. This rejection is respectfully traversed.

It is well known in the art that the formulation of venlafaxine is particularly difficult because of its extremely high solubility and the existence of what is known as the "burst effect" or "burst phenomenon" (see the detailed discussion and supporting evidence below). Because of these special problems, those of ordinary skill in the art would not consider that standard techniques, such as those described by Oshlack that are used for the formulation of water insoluble or slightly water soluble pharmaceuticals, will necessarily solve the problems of obtaining extended release formulations of venlafaxine.

After the effective filing date of the present invention, several groups around the world have filed patent applications attempting to resolve the problems of formulating venlafaxine into an extended release formulation. Some of these actually have derived solutions very similar to that of the

present invention, but all of them considered their solutions to be sufficiently novel to warrant the filing of patent applications. All foreign patents and non-patent literature referred to below are being submitted on even date herewith to serve as evidence supporting the arguments for non-obviousness.

With respect to the known problems in formulating venlafaxine, reference is first made to the Sherman European patent which is relied upon by the examiner in this rejection. At page 3, lines 34 to 35, Sherman reports:

> It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride in venlafaxine proved to be extremely water soluble.

US2006/0182797 to Karavas states at paragraph [0003]:

> An objective of the present study is to provide a sustained release formulation which is free of the increased release of the drug observed at the initial stages of release that occurs in sustained release systems containing water soluble drugs such as venlafaxine HCl, known as burst phenomenon.

U.S. Patent 7,807,195 to Bhattacharya states at column 1, lines 50-53:

> Venlafaxine hydrochloride is very soluble in water. It is known that it is very difficult to develop a pharmaceutical form

> with a very slow dissolution rate of freely soluble drug.

US2006/01211114 to Antarkar states in the first sentences of paragraph [0004]:

> Venlafaxine HCl is highly water-soluble and has a potential problem of dose dumping and burst effect when using a controlled release matrix …. It is thus desirable to develop dosage forms of Venlafaxine HCl to ensure consistent delivery and prolonged plasma levels, with insignificant contribution to the initial release in case of a failure of the system, thereby avoiding dose dumping.

WO2005/034930 to Fekette states in the paragraph bridging pages 4 and 5 that active ingredients of extremely high solubility are disadvantageous from the viewpoint of the layering pelletization. In the second full paragraph on page 10, Fekette states that venlafaxine hydrochloride belongs to the group of active ingredients readily soluble in water (0.57g/ml), and then goes on to speak about problems known in the prior art in formulating active ingredients which are so soluble. The paragraph beginning at line 3 of page 12 states:

> Data of the technical literature show that in case of the readily water-soluble venlafaxine hydrochloride experts have so far failed to elaborate a composition of the excipients enabling the preparation of pellets having a high active ingredient content and suitable quality (being

> approximately spherical in shape) and providing an advantageous product fraction.

U.S. Patent 7,563,456 to Rafael states at column 1, lines 38-40:

> The elaboration process further avoids an additional difficulty that presents the Venlafaxine in programmed liberation preparations, such as its high solubility.
>
> Various publications also speak about the burst

effect. Note Dias et al. 2006, where it states in the second paragraph:

> The high water solubility of drugs (eg venlafaxine HCL has a solubility of 572 mg/mL), leads to an initial burst release from HPMC matrixes.

Oshlack is not concerned with solving the problems of burst phenomenon. Oshlack optimizes the method of application of an aqueous dispersion of a hydrophobic polymer - ethylcellulose - onto beads or minitablets to provide a controlled release profile. In Oshlack's examples, he does not use venlafaxine. His drugs are not very soluble. Indeed at column 14, line 7-11, Oshlack indicates that the active agent can include both water-soluble and water-insoluble drugs. Clearly, one trying to solve problems involved when formulating a highly water-soluble drug, subject to the burst phenomenon, would not turn to Oshlack for solutions. Oshlack is not trying

to solve the same problem. Indeed, the only place in the Oshlack specification that talks about a barrier layer is column 9, lines 56-64. This minor disclosure in part of a larger specification that does not deal with the problems of highly soluble active agents, does not provide motivation for using a barrier layer in an attempt to solve the burst phenomenon problem known for highly water soluble active principles such as venlafaxine. Indeed, Oshlack only uses a barrier coating on occasion - not routinely.

What drives Oshlack is the application of an aqueous ethyl cellulose coating and the subsequent need to cure the beads or minitablets at elevated temperatures very quickly after coating in order to stabilize them, i.e., dry them out. There is no suggestion that such a technique would work when using an extremely water-soluble active ingredient such as venlafaxine hydrochloride.

In the Palomo Coll patent, the active ingredient is omeprazole and it is rapidly decomposed at neutral or acidic pH. That forces the formulator to stabilize the formulation in such a way as to protect the drug as it passes through the gastric environment into the small intestine where it is 100% released and absorbed into the blood stream. Palomo Coll formulated the

drug into a matrix pellet in order to minimize the surface area exposure of the drug as most would be embedded in the matrix rather than being on the surface of the pellet. Palomo Coll was then forced to put on a first coating in order to protect the small percentage of omeprazole that was on the matrix surface. The first coating was a basic water soluble excipient and a basic organic compound. This would have protected the active ingredient until it reached the target pH environment in the GI tract. The outer coating was just an enteric coating to make sure it passed through the gastric environment in a bioavailable form.

Accordingly, the rationale for putting the first coat onto the pellets was an entirely different circumstance, i.e., the unique properties of the active ingredient, omeprazole, necessitated that it be protected from acid pH. Scientifically, none of these teachings are applicable to venlafaxine hydrochloride. Focusing on the functionality of the active ingredient drives the formulators' mindset of why to use any given ingredients and layers. Omeprazole differs from venlafaxine in that it is rapidly decomposed at neutral or acid pH. That is not the case for venlafaxine. The latter is very soluble and very stable. The functionality driver for

omeprazole is to further protect the active ingredient that is on the surface of the matrix pellets from acid pH. There is nothing in any of the references of record which would suggest that the barrier coating of Palomo Coll would necessarily be useful in solving the burst phenomenon, which is a well-known problem when attempting to make extended release formulations of venlafaxine hydrochloride.

In light of this analysis of the state of the prior art, it is apparent that one of ordinary skill in the art would not have been able to predict *ab initio* which of the infinite number of formulation techniques that were known at the time of the present invention would permit one to overcome the burst phenomenon problem for this particular drug and arrive at an extended release formulation that releases venlafaxine hydrochloride in a pH-independent manner over an approximately 24 hour period after oral administration, and particularly one that is bioequivalent to the brand formulation.

Accordingly, no *prima facie* case of obviousness has been established as the examiner has not established that there would have been a reasonable predictability of success in overcoming the disadvantages of the extremely high solubility of venlafaxine hydrochloride, recognized by the Sherman reference

and the others discussed above, by using standard techniques developed for completely different drugs in order to make enteric formulations, as opposed to a pH independent extended release formulation as presently claimed.

For all of these reasons reconsideration and withdrawal of this rejection are earnestly solicited.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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